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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,014	11/22/2000	Kyriacos A. Mitraphanous	550 184	4760

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EXAMINER
GUZO, DAVID

ART UNIT	PAPER NUMBER
1636	10

DATE MAILED: 03/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/701,014	MITRAPHANOUS ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 11/21/00 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. .

This rejection is maintained for reasons of record in the previous Office Action (Paper #7) and for reasons outlined below. It has been applied to new claim 31 as a result of applicants' amendment filed 1/8/03.

Applicants traverse this rejection by asserting that the examiner has improperly read gene therapy use limitations into the claim. Applicants assert that the pending claim reads on a pharmaceutical composition and not a gene therapy method. Applicants assert that the instant specification provides sufficient teachings to enable the skilled artisan to prepare the claimed pharmaceutical composition and use it to transduce target neuronal cells selectively.

3. Applicant's arguments filed 1/8/03 have been fully considered but they are not persuasive. Applicants claim a **pharmaceutical** composition comprising the instant rabies G glycoprotein pseudotyped retroviral vectors. A pharmaceutical composition is, by definition, a medicament or therapeutic composition which elicits a beneficial or therapeutic effect in a subject to whom the pharmaceutical composition is administered. An examination of the instant specification

indicates that the **only disclosed use for a pharmaceutical composition comprising the recited pseudotyped retroviral vectors is for gene therapy**. Therefore the claimed pharmaceutical composition must be read as a gene therapy composition because the only disclosed use for the composition is for practicing gene therapy. The examiner agrees with applicants with regard to the skilled artisan being able to make the claimed pharmaceutical composition; however, 35 USC 112, 1st paragraph requires that the skilled artisan disclose how to make **and use** the claimed invention. A composition for which there is no disclosed enabled use is itself not enabled.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent filed by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 21-24, 26-30 and 34-39 are rejected under 35 U.S.C. 102(e) as being anticipated by Bremel et al.

This rejection is maintained for reasons of record in the previous Office Action and for reasons outlined below. The rejection is applied to new claims 21-24, 27-30 and 34-39 as a result of applicants' amendment filed 1/8/03.

Applicants' traverse this rejection by asserting that the claimed retroviral vector delivery system differs from that disclosed by Bremel et al. in that the claimed vectors selectively transduce neuronal cells at higher efficiencies than in non-neuronal cells. Applicants argue that Bremel et al. teaches retroviral vectors which are adapted for transducing oocytes wherein all the cells of the resulting organism comprise the transgene. Applicants further assert that Bremel et al. teach away from the instant invention in that the vectors disclosed by Bremel et al. are used for transduction of oocytes and not neuronal cells.

Applicant's arguments filed 1/8/03 have been fully considered but they are not persuasive. Applicants' primary argument is that the claims, as now amended, recite a retroviral vector delivery system which transduces neuronal cells at higher efficiencies than non-neuronal cells. This ability is a result of the pseudotyping of retroviral vectors with the rabies G glycoprotein. It is noted however, that rabies virus is a well known neurotropic virus wherein the cell tropism for neuronal cells is regulated by the rabies G glycoprotein (the only rabies protein expressed on the outside of the viral envelope). References by Gaudin et al. (Virology, 1992, Vol. 187, pp. 627-632) and Morimoto et al. (PNAS, March 1998, Vol. 95, pp. 3152-3156) are cited to show that the skilled artisan would have been aware of these well known inherent properties of rabies viruses. Therefore, a retrovirus pseudotyped with the rabies G glycoprotein (as disclosed by Bremel et al.) would inherently possess a greater tropism for neuronal cells than a retrovirus without the rabies virus G glycoprotein. With regard to applicants' arguments that the retroviral vectors disclosed by Bremel et al. are somehow different from the instantly claimed vectors because they

are adapted for use in transducing oocytes, it is noted that the description of the pseudotyped retroviral vectors in columns 6-10 of Bremel et al. pertains to pseudotyped retroviral vectors which can be used to transduce any host cell of choice (including human cells), cells transduced with the vectors and methods of altering the infection profile (i.e. altering the host range) of a retrovirus by pseudotyping with rabies G protein or other G proteins. Bremel et al. therefore teaches the claimed invention. With regard to the citation of the Gaudin et al. and Morimoto et al. references, it is noted that secondary teachings or extrinsic evidence can be cited in a 35 USC 102 rejection to show that a characteristic not disclosed in the reference is inherent (See MPEP 2131.01).

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bremel et al. in view of Olsen et al.

This rejection is maintained for reasons of record in the previous Office Action and for reasons outlined below. The rejection includes claim 25 as a result of applicants' amendment filed 1/8/03.

Applicants traverse this rejection by re-asserting that Bremel et al. does not teach retroviral vectors pseudotyped with rabies G protein that more efficiently transduce neuronal cells compared with non-neuronal cells. Applicants argue that neither Bremel et al. nor Olsen et al., individually or together, suggest the claimed invention and that there is no motivation to combine the teachings of Olsen et al. on pseudotyping EIAV with the VSV G protein with the teachings of Bremel et al. on pseudotyping retroviral vectors with rabies G protein. Applicants also argue that because Bremel et al. teaches that the VSV and rabies G proteins have a high degree of sequence conservation the substitution of the rabies G protein for the VSV G protein would not significantly alter the host range and the transduction selectivity of the vector.

Applicants' arguments have been considered but are not persuasive. The inherent ability of retroviral vectors pseudotyped with the rabies G protein to selectively transduce neuronal cells at higher efficiencies than non rabies G pseudotyped retroviral vectors has been discussed in the examiner's response to applicants' remarks traversing the above 35 USC 120(e) rejection. With

regard to the lack of motivation to combine the teachings, it is noted that Bremel et al. teaches that any retroviral vector, including lentiviruses such as HIV (EIAV is also a lentivirus), can be pseudotyped with envelope glycoproteins such as rabies G protein so as to alter the host range of the viruses and improve the versatility of the vectors. Olsen et al. also teaches that EIAV can be pseudotyped with any non-EIAV envelope protein so as to alter the host range of the virus. Given that rabies G protein was well known to target neurons, and is specifically disclosed by Bremel et al. as a specific pseudotyping envelope protein for any retrovirus vectors, it must be considered that Olsen et al.'s teaching that EIAV can also be pseudotyped with any non-EIAV envelope protein to alter host range would motivate the ordinary skilled artisan to pseudotype EIAV vectors with the rabies G protein to achieve the expected result of altering the host range of the EIAV retrovirus vector. It would have been obvious to do this because both references teach using retroviral vectors pseudotyped with non-retroviral envelope proteins so as to alter the host ranges of the vectors. With regard to applicants' assertion that the similarities between the G proteins from VSV and rabies virus would mitigate against substituting the rabies G protein for the VSV G protein, it is again noted that the rabies G protein was well known (unlike VSV) to selectively target neurons and would therefore expand the host range of EIAV vectors to neurons. For the reasons of record and for reasons cited above, the rejection is maintained.

8. Claims 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bremel et al.

Applicants claim methods of selectively transducing (or delivering nucleic acids to) neuronal cells comprising contacting retroviral vectors pseudotyped with the rabies G protein with the cells wherein said neuronal cells are transduced with higher efficiencies than non-neuronal cells.

Bremel et al. is applied as in the above 35 USC 102(e) rejection. Briefly, Bremel et al. discloses the rabies G protein pseudotyped retroviral vectors used in the claimed methods. The rabies G protein pseudotyped vectors disclosed by Bremel et al. inherently have a tropism for neurons. While Bremel et al. does not specifically teach a method for specifically transducing or delivering nucleic acids to neuronal cells using the pseudotyped retroviral vectors, it would have been obvious for the ordinary skilled artisan to use the rabies G protein pseudotyped vectors to transduce neuronal cells because the natural tropism (governed by the G protein) of the rabies virus is neurons. Since the teachings of Bremel et al. are directed to altering the host range of retroviral vectors by pseudotyping, the obvious reason for pseudotyping retroviral vectors with a protein (rabies G protein) which naturally targets rabies virus to neurons would be to target retroviral vectors (pseudotyped with the rabies G protein) to neurons. One of ordinary skill in the art would have been motivated to transduce neuronal cells with the recited pseudotyped retroviral vectors because rabies G protein was known to target the virus to neurons and pseudotyping retroviral vectors with this protein would result in retroviral vectors capable of preferentially infecting neurons. Given the teachings of the art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered that the

ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

It is noted that the rabies G glycoprotein has been extensively studied, the functional portions of the molecule delineated and numerous mutants, variants and derivatives have been made in the prior art. Applicants cite some of the prior art concerning rabies G glycoprotein on pp. 14-16 of the specification.

No Claims are allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate .

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David Guzo
March 13, 2003

DAVID GUZO
PRIMARY EXAMINER